II. REMARKS

Formal Matters

Claims 1-12 and 15-19 are pending after entry of the amendments set forth herein.

Claims 1-12 and 15-19 were examined. Claims 6-8 and 15-18 were rejected. Claim 19 was objected to as being dependent on a rejected claim, but otherwise allowable. Claim 19 is amended to make it independent form, and, as such, this objection is mooted.

As no new matter has been added by the above amendments, their entry is respectfully requested.

The Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Allowable subject matter

The Applicants gratefully acknowledge the Examiner's indication that claim 19 is allowable. Claim 19 is amended to be in independent form, and, as such, an allowance for claim 19 is respectfully requested.

Withdrawal of rejections

The Applicants gratefully acknowledge the Examiner's withdrawal of the following rejections: the rejection of claim 6-8 and 15-17 under 35 U.S.C. §112, first paragraph, the rejection of claims 7 and 16 under 35 U.S.C. §112, second paragraph and the rejection of claims 6-8 and 15-17 under 35 U.S.C. §102(b) over Kourilsky.

Rejection under 35 U.S.C § 103

The Office Action stated that claims 6-8 and 15-18 are rejected under 35 U.S.C § 103 as obvious over Kourilsky in view of Guo. Specifically, the Office Action asserts one of skill in the art would incorporate Kourilsky's urea-based hybridization methods into Guo's oligonucleotide array methods to provide the claimed invention. The Applicants respectfully traverse the rejection.

According to MPEP §2142, an examiner must meet three basic criteria to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (2) there must be a

reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations.

As such, a motivation to combine is essential for a *prima facie* case of obviousness to be made.

Furthermore, with regard to rejections based on obviousness, the MPEP at §2143.02 states "The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success." As such, in order to establish a *prima facie* case of obviousness, a reasonable expectation of success is required.

Also with regard to rejections based on obviousness, the MPEP at § 2141.02 teaches that a prior art reference must be considered in its entirety, including disclosures that *teach away* from the claimed invention.

As will be discussed in greater below, there is no motivation to combine the Guo and Kourilsky, and, in fact, Guo teaches away from the claimed invention by stating that low melting temperature oligonucleotides are undesirable and that higher hybridization temperatures for his assays are desirable. Furthermore, because of the inherent differences between the large DNA molecules taught by Kourilsky and the oligonucleotides taught by Guo, a skilled person would not combine these references with a reasonable expectation of success. As such, withdrawal of this rejection is respectfully requested.

Kourilsky's hybridization methods involve pulse-labeled phage lambda mRNA and phage lambda DNA that is immobilized on a Sartorius filter. Since phage lambda DNA is approximately 50 kb (i.e., 50,000 bp) in size and Sartorius filters are not glass, Kourilsky fails to disclose a method involving an oligonucleotide probe attached to the surface of a glass substrate. Guo's hybridization methods involving oligonucleotides attached to the surface of a glass slide.

Kourilsky expresses no desire to use oligonucleotide probes or a glass substrate in his assays. As such, Kourilsky provides no motivation to combine his teachings with Guo. Similarly, Guo expresses no desire to lower the hybridization temperature used in his methods, and fails to provide any suggestion that his hybridization buffers may be modified by the addition of T_m-lowering compounds like urea. As such, Guo, like Kourilsky, provides no motivation to combine the cited references. In other words, neither Guo nor Kourilsky provide any motivation to combine their respective teachings to provide the claimed invention.

Furthermore, Guo, in the second and third paragraphs in the section entitled "Design of ASO sequences" on page 5460, appears to teach away from lowering the melting temperature of his assays. Guo states, at the bottom of the third paragraph of this section that "Although all three lengths yielded approximately equal hybridization signals, single-base mismatch discrimination was best achieved with the 15-mer, whereas the 20-mer showed no reproducible discrimination and the 12 nucleotide sequence was difficult to use *due it its low melting temperature* (data not shown)." (emphasis added). Guo also indicates that *increasing*, (i.e., not *decreasing*) the melting temperature of his assays is desirable. Guo's desire is stated in the last sentence of the second paragraph which reads "This concern may be addressed in part by choosing longer ASO sequences, permitting *higher temperatures* to be employed in hybridization and therefore melting out internal structures in the single-stranded PCR products." Guo therefore indicates a lack of a desire to reduce the melting temperature of an oligonucleotide, and, indeed, appears to indicate a desire to actually *increase* the melting temperature of an oligonucleotide to remove internal secondary structure. This represents a teaching away from the claimed invention, which is directed to methods that *decrease* the melting temperature of an oligonucleotide.

Furthermore, Kourilsky and Guo cannot be combined with any reasonable expectation of success.

Kourilsky discloses hybridization assays that involve phage lambda DNA molecules. Since phage lambda DNA is approximately 50,000 contiguous nucleotides (i.e., 50 kb) in length, Kourilsky's methods involve DNA molecules that are approximately 50,000 nucleotides in length. Guo's method, on the other hand, involve oligonucleotide DNA molecules that are 12, 15 or 20-mers (see the third paragraph of the section entitled "Design of ASO sequences" on page 5460). Of the three sizes of oligonucleotides, Guo's preferred oligonucleotides are 15-mers. As such, Guo's method involve DNA molecules that are 12-20 nucleotides in length.

A skilled person would not combine the methods of Kourilsky and Guo because DNA molecules of 50,000 nucleotides in length and DNA molecules of 12-20 nucleotides in length have very different hybridization characteristics. In other words, the thermodynamic stability of nucleic acid duplexes 50,000 nucleotides in length is much greater then the thermodynamic stability of nucleic acid duplexes of 12-20 nucleotides in length, and, as such, a skilled person would have no reason to think that a compound (i.e., urea) that alters the

thermodynamic stability of a duplex of a 50,000 nucleotide DNA duplex would alter the thermodynamic stability of a duplex of a 12-20 nucleotides in length.

Evidencing this assertion are sections from two frequently used laboratory manuals, usually referred to as "Maniatis" and "Ausubel" (*Sambrook, et al, Molecular Cloning: A Laboratory Manual, Third Edition, (2001) Cold Spring Harbor, N.Y.* and *Ausubel, et al, Short Protocols in Molecular Biology, 3rd ed., Wiley & Sons, (1995)*, respectively), attached herewith as Exhibits A and B. Maniatis discusses a formula for calculating the effect of another hybridization temperature-reducing agent, salt, on the hybridization temperature of a DNA. Maniatis states: "The above equations apply only to hybrids greater than 100 nucleotides in length". (highlighted in Exhibit A). Maniatis therefore indicates that larger DNA molecules (as taught by Kourilsky) and smaller DNA molecules (as taught by Guo), have different hybridization characteristics that are not governed by this formula. Maniatis's teachings are reflected in Ausubel, which provides two different hybridization protocols for large and small DNA molecules (Exhibit B, section titles highlighted). The Applicants submit that if the same methods could be used for both large and small DNA molecules, Ausubel's hybridization protocols would not be divided in two sections. As such, both Maniatis and Ausubel indicate that large and small DNA molecules have different hybridization characteristics and often require different methods. In view of this, a skilled person would no expectation that urea, which had previously been used as a hybridization temperature reducing agent only for *large* DNA molecules, would be effective as a hybridization temperature reducing agent for *small* DNA molecules.

Finally, the Examiner states that the urea-based hybridization methods of Kourilsky would be incorporated into the oligonucleotide/glass slide methods of Guo because of comments made by Guo in the last paragraph of page 5456. In this paragraph, Guo extols the virtues of "Format II" arrays (i.e., panels of oligonucleotides arrayed on a support for polymorphism analysis). At best, this paragraph indicates the desirability of arrays of oligonucleotides for polymorphism analysis. Since the paragraph does not express the desirability of reducing the hybridization temperature in an array assay, the Applicants respectfully submit that Guo's paragraph would not motivate a skilled person to add urea to Guo's hybridization buffer.

In summary, since Guo teaches away from the claimed invention, and, because Maniatis and Ausubel teach that large and small DNA molecules behave very differently and

often require different methods for their use, a skilled person would find no motivation to combine the references of Kourilsky and Guo. As such, the Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

In view of the foregoing, withdrawal of this rejection is respectfully requested.

OIPE JC14
JUL 07 2003
PATENT & TRADEMARK OFFICE

RECEIVED
JUL 11 2003
TECH CENTER 1600/2900

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone Timothy Joyce at (650) 485 4310.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 that may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 7-7-03 By: James S Keddie
James S. Keddie, Ph.D.
Registration No. 48,920

Date: 7.7.03 By:
Bret E. Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\AGIL\083 (10010819-1)\10010819 response to oa 5-31-2003.doc